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Overview on the Fungal Metabolites Involved in Mycopathy

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Abstract

This review presents several types of metabolites produced by the most common fungal pathogens and their roles in fungal pathogenesis. Toxic metabolites from toxigenic fungi include compounds such as aflatoxins, trichothecenes, ochratoxins, fumonisins, zearalenone and ergot alkaloids, which display hepatotoxicity, nephrotoxicity, neurotoxicity and genotoxicity. The ability of fungi to produce and elaborate hydrolytic enzymes is associated with virulence of several pathogenic fungi. The biogenesis of siderophores is investigated as it is a mechanism of iron acquisition. In particular, these metabolites act as iron chelators and storage compounds to support pathogenic fungi to survive in mammalian hosts whose iron homeostasis is strictly regulated and prevent the formation of free radicals which are formed by free iron. Melanins clearly promote infectivity in a number of species of fungal pathogens. They interfere with oxidative metabolism of phagocytosis making the fungus relatively resistant to phagocyte attack. Several metabolies such as pullulan, mannitol, β-(1,3)-glucan, hem-binding proteins, estrogen-binding proteins, farnesol, agglutinin-like sequence proteins, glucuronoxylomannan and others also have advantages in fungal pathogenicity. The identification of fungal metabolites involved in pathogenesis, and recognition of mechanisms of pathogenesis may lead to development of new efficient anti-fungal therapies.

Keywords

Fungal Metabolites; Pathogenesis; Mycotoxicoses; Mycoses

1. Introduction

Fungi are ubiquitous, eukaryotic microorganisms which found in many different environments wherever organic material is available. They are found in a wide range of environments due to their capacity to utilize a variety of

substrates and to their relative tolerance to low pH, low water activity and low temperature [1]. A number of fungi are symbiotic and may live in commensalism, mutualism or parasitism with other organisms. However, only some of the fungal species are pathogenic to man. Human fungal pathogens belong to four main groups, namely zygomcetes, ascomycetes, deuteromycetes and basidiomycetes [2]. Fungi can synthesize a vast diversity of chemical compounds either of primary or secondary metabolism origin. Contrary to primary metabolites, secondary metabolites are not necessary for normal growth or development, but often have potent physiological activities [3]. These metabolites are of a great importance to humankind due to their involvement in pathogenicity [4]. Most fungal secondary metabolites are produced after the fungus has completed its initial growth phase [5]. According to chemical structure, fungal secondary metabolites may be polyketides (e.g. aflatoxin and fumonisins), non-ribosomal peptides (e.g. sirodesmin, peramine and siderophores such as ferricrocin), terpenes (e.g. T-2 toxin and deoxynivalenol), or indole terpenes (e.g. paxilline and lolitrems) [6]. Toxic metabolites from fungi include compounds such as aflatoxins, trichothecenes, ochratoxins, fumonisins, zearalenone, ergot alkaloids and others [7]. Some fungi can produce iron chelators (siderophores) such as hydroxamates to solubilize Fe(III) to make it available for uptake [8]. Other fungal metabolites such as melanins, enzymes, carotenoids and others have also been described. Exposures to toxic fungal metabolites (mycotoxins) produce diseases collectively called mycotoxicoses, while growth of fungi on human and animal results in diseases collectively called mycoses [7]. This review deals with various metabolites synthesized by fungi having significance roles in mycopathy.

2. Virulence, Pathogenicity and Mycopathy

Mycologists estimate that there are 100,000 species of fungi in nature. However, only about 300 species have been linked to diseases in humans and animals. In general, the term pathogenicity refers to the ability of an organism to cause disease. This property is the result of a direct interaction between the pathogen and the host. In many ways, pathogenicity and virulence are very broadly defined terms. With the exception of a few dermatophytes, pathogenicity among the fungi is not necessary for the maintenance or dissemination of the species [9]. Mycopathy is a collective term used for diseases caused by fungi either living or dead or their metabolic products (toxins, allergins or enzymes). This complex term comprises disease manifestations such as mycotoxicosis and mycoses [10]. Mycotoxicoses occur when mycotoxins enter the body, usually by consumption of contaminated feed. Mycotoxicoses are not contagious and mycotoxins do not stimulate the immune system. On the other hand, mycoses occur when fungi infect tissues of the body. Mycosis can be contagious and may lead to stimulation of the immune system. Fungal pathogens can enter the body through respiratory, mucous and cutaneous routes. Immunity to fungal infections consists of nonspecific barriers, inflammation and cell-mediated immune responses [11]. Several determinants including genes or gene products known as virulence factors are involved in this relationship, producing superficial to invasive infections in humans [2] [9]. Virulence factors are molecules that enable pathogen to achieve colonization of host tissues (this includes adhesion to cells), evasion and/or inhibition of the host's immune response. Fungal pathogens possess a wide array of virulence factors. Some of them are produced and secreted to the tissue environment of the host, and others may remain inside the fungus or as structural molecule but have roles in fungal pathogenicity. Furthermore, the ability of an organism to adapt quickly to new environmental challenges is itself likely to be an effective virulence mechanism, in that it enables the pathogen to take advantage of new opportunities [12] [13].

3. Fungal Metabolites Involved in Mycotoxicoses

Mycotoxicosis is the term used for intoxication associated with exposures to mycotoxins [7] [14]. The term mycotoxin simply means a toxin produced by a fungus. Mycotoxins are low-molecular weight natural products produced as secondary metabolites by toxigenic species of microscopic filamentous fungi, which can cause toxic effects in humans and animals [7] [15] [16]. These toxins have no biochemical significance in fungal growth and development [17]. Toxigenic molds are known to produce one or more of these toxic secondary metabolites. Several types of fungal species of *Fusarium*, *Aspergillus*, *Penicillium*, *Cladosporium*, *Claviceps*, *Alternaria* and *Helminthosporium* have been reported to produce mycotoxins [18]. One mold species may produce many different mycotoxins, and the same mycotoxin may be produced by several species. Mycotoxins can be clinically classified into hepatotoxins, nephrotoxins, neurotoxins, immunotoxins and others [7]. They are present in many

food items of vegetable and animal origin as well as in the air [19]. In low concentrations, mycotoxins are toxic and introduced to humans via ingestion, contact and inhalation [20]. On the other hand, other low-molecular weight fungal metabolites such as ethanol that are toxic only in high concentrations are not considered mycotoxins [21]. Contamination of food with mycotoxins is caused either by direct contamination of grains, fruits and their products or by "carry-over" of mycotoxins and their metabolites in animal tissues, milk and eggs after intake of contaminated feedstuff [22]. About 300 - 400 mycotoxins are known, but most of them do not have an impact on the health of human and animal beings, simply because they do not occur in substantial amounts in foods and feeds [23]. The mycotoxins that pose the greatest potential risk to human and animal health as food and feed contaminants are aflatoxins, trichothecenes, fumonisins, zearalenone, ochratoxin A and ergot alkaloids [7] [24]. These toxins and their major toxigenic species of fungi are presented in **Table 1**. However, other mycotoxins should be included because of their frequency of occurrence in commodities or their products or their co-occurrence with other important mycotoxins. This expanded list includes cyclopiazonic acid, sterigmatocystin, gliotoxin, citrinin, penitrems, patulin and miscellaneous mycotoxins such as fusarin C, fusaric acid, penicillic acid, mycophenolic acid, roquefortine, PR toxin and others [24]. Mycotoxicosis can be categorized as acute or chronic. Generally, acute toxicity has a rapid onset and an obvious toxic response, while chronic toxicity is characterized by low-dose exposure over a long time period, resulting in cancers and other generally irreversible effects [25].

3.1. Aflatoxins

Aflatoxins are one of the most potent mycotoxins produced by fungi *Aspergillus flavus* and *A. parasiticus* in/on foods and feeds [26], and another producers have been reported [27] [32]. Aflatoxins were first isolated and characterized after outbreaks of disease and death in turkeys (turkey × disease) and cancer in rainbow trout fed on rations formulated from peanut and cottonseed meals [33]. Based on chemical structure, aflatoxins are difuranocoumarin derivatives produced by a polyketide pathway by many fungal-strain producers [7]. The diseases caused by aflatoxins consumption are called aflatoxicoses, which reported in humans in many parts of the world. Aflatoxins can cause acute and chronic health effects including immune suppression, growth retardation, cancer and, in severe acute exposure, death [34]-[37]. Aflatoxins can cause disease throughout the body, but are most commonly known for causing acute or chronic liver disease and liver cancer. On the basis of acute toxicity, aflatoxins are considered among the most potent hepatotoxins within the different variants and are by far the most studied [38]. There are six major chemical forms of the aflatoxins, including aflatoxins B1, B2, G1, G2, M1 and M2 [39]. Aflatoxins B1 and B2 fluoresce blue under shortwave UV, while aflatoxins G1 and G2 fluoresce green. Aflatoxins M1 and M2 are the forms that B forms are converted to through metabolic processes in animals and are excreted in milk [14]. Aflatoxin B1 (**Figure 1**) is the most potent natural carcinogen known [40], and is usually the major aflatoxin produced by toxigenic strains [7]. Hepatocarcinogenicity of aflatoxins are mainly attributed to adduct formation with DNA, RNA and protein. In addition, aflatoxins also cause lipid peroxidation as well as oxidative damage to DNA [41] [42].

3.2. Trichothecenes

Trichothecenes are a family of mycotoxins which include over 180 structurally-related compounds produced by several fungal genera, especially *Fusarium*, *Stachybotrys*, *Trichothecium*, *Trichoderma*, *Memnoniella*, *Phomop-*

Table 1. The major mycotoxins and their producers.

| Mycotoxin	Fungal species
Aflatoxins	*Aspergillus flavus, A. parasiticus, A. nomius, A. tamarii, A. pseudotamarii, A. bombycis, A. ochraceoroseus*
Trichothecenes	*Fusarium, Stachybotrys, Trichothecium, Trichoderma, Memnoniella, Phomopsis, Myrothecium*
Ochratoxins	*Aspergillus ochraceus, A. carbonarius, Penicillium verrucosum.*
Fumonisins	*F. verticillioides, F. proliferatum*
Zearalenone	*F. graminearum, F. culmorum F. equiseti F. crookwellense*
Ergot alkaloids	*Claviceps purpurea*
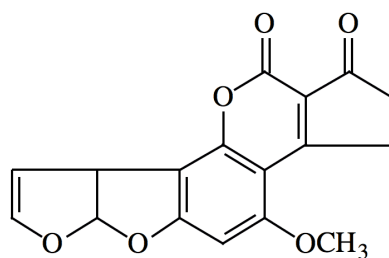
Figure 1. The chemical structure of aflatoxin B1.

sis and *Myrothecium* [43]-[46]. Chemically, they are sesquiterpene compounds that consist of the trichothecene core with epoxy rings at C-12 and -13 positions. All trichothecenes contain a common 12,13-epoxytrichothene skeleton and an olefinic bond with various side chain substitutions [7]. According to the presence of a macrocylic ester or an ester-ether bridge between C-4 and C-15, trichothecenes are classified into macrocylic and non-macrocyclic trichothecenes [47]. *Fusarium* is the major genus implicated in producing the non-macrocylic trichothecenes [7]. From a public health perspective, trichothecenes belonging to three structural groups appear to be most important: type A trichothecenes which have isovaleryl, hydrogen, or hydroxyl moieties at the C-8 position (e.g., T-2 toxin), Type B trichothecenes which have a carbonyl group at the C-8 position (e.g., deoxynivalenol) and the Type D (macrocyclic trichothecenes), which have a cyclic diester or triester ring linking C-4 to C-15 (e.g., satratoxin G) [48]. Trichothecenes are commonly found world-wide on cereals such as wheat, rye, barley, oats and corn [49]. T-2 toxin (**Figure 2**) is the most toxic type A trichothecene [50]. Trichothecenes have been associated with human health hazards and the reported health implications range from nausea, vomiting, skin irritation and internal bleeding to respiratory disorders of various kinds [51]. T-2 toxin can cause severe skin irritation (erythema, edema and necrosis) and vesication [52]. Deoxynivalenol (**Figure 3**) can cause immune stimulation and suppression in leukocytes by upregulating gene expression and apoptosis, respectively [53]. Deoxynivalenol inhibits intestinal cell proliferation and is absorbed through the intestinal epithelium by simple diffusion [54]. In addition, trichothecenes can activate inflammatory response in human macrophages [55]. Trichothecenes have also been linked to indoor air illness [56]-[58]. Mechanistically, trichothecenes are powerful inhibitors of protein synthesis, inhibition of mitochondrial function and they can interact with the cell membrane [24] [46]. They bind to the peptidyl transferase center of the 60S ribosomal subunit and prevent polypeptide chain initiation or elongation [59] [60]. In addition, it is known that trichothecenes rapidly activate mitogen-activated protein kinases and induce apoptosis in a process known as the "ribotoxic stress response" [61]-[64].

3.3. Ochratoxins

Ochratoxins are a family of chemically related mycotoxins produced by several species of *Aspergillus* and *Penicillium* [65]. Chemically, they are pentaketides made up of dihydroisocoumarin linked to L-β-phenylalanine [66]. Ochratoxins consists of three members, A, B and C that differ slightly from each other in chemical structures. These differences, however, have marked effects on their respective toxic potentials. The most important and most toxic ochratoxin found naturally in food is ochratoxin A (**Figure 4**) [67] [68]. It was first discovered in 1965 in an *Aspergillus ochraceus* isolate [69]. It is also produced by *Penicillum verrucosum* during the storage of cereals, cereal products and other plant-derived products [70]. Ochratoxins contamination of foods and feeds poses a serious health hazard to animals and humans [66]. Ochratoxin A has been shown to be nephrotoxic, hepatotoxic, teratogenic, carcinogenic, genotoxic and immunosuppressive [66] [71] [72]. The primary effects of ochratoxin A are associated with the enzymes involved in phenylalanine metabolism, mostly by inhibiting the enzyme involved in the synthesis of the phenylalanine tRNA complex [73]. In addition, it inhibits mitochondrial ATP production [74] and stimulates lipid peroxidation [75]. Ochratoxin A is believed to be responsible for a human disease called endemic Balkan nephropathy [76] [77], which is a form of interstitial nephritis that occurs among several small, discrete communities along the Danube River and its major tributaries, in the modern countries of Croatia, Bosnia and Herzegovina, Serbia, Romania and Bulgaria [7] [78].
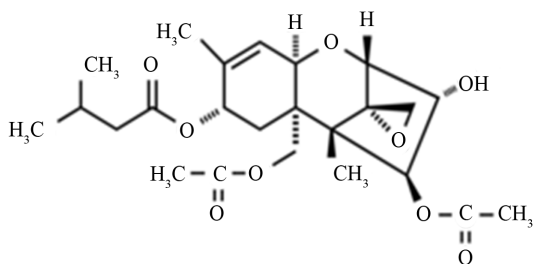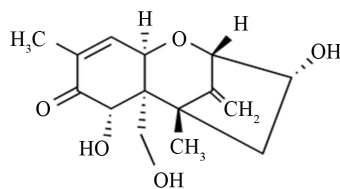
Figure 2. The chemical structure of T-2 toxin.
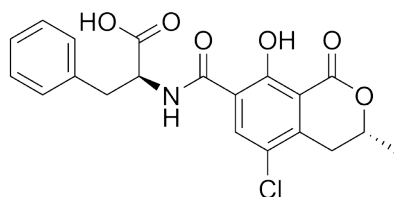

Figure 3. The chemical structure of deoxynivalenol.

Figure 4. The chemical structure of ochratoxin A.

3.4. Fumonisins

Fumonisins are a group of mycotoxins produced by fungi of the genus *Fusarium* such as *F. verticillioides* and *F. proliferatum* [79]. Another producers rather than *Fusarium* have been reported and there are about 53 different fumonisins [80], but fumonisins B1 (**Figure 5**), B2 and B3 are all carcinogenic and regarded as the most important [81] [82]. Generally, the human health problems related to fumonisins are almost exclusively associated with the consumption of contaminated maize or products made from maize [83]. The main effects of fumonisins include inhibition of ceramide synthase, causing accumulation of bioactive intermediates of sphingolipid metabolism (sphinganine and other sphingoid bases and derivatives) in many types of cells and tissues, including hepatocytes, neurons and renal cells as well as depletion of complex sphingolipids, which interferes with the function of some membrane proteins, including the folate-binding protein (human folate receptor alpha) [84] [85]. There has been findings that fumonisins are suspected risk factors for esophageal [83] and liver [60] cancers, neural tube defects [84] [86] and cardiovascular problems [87] in people consuming relatively large amounts of food made with contaminated maize.

3.5. Zearalenone

Zearalenone (**Figure 6**) is a polyketide mycotoxin with potent estrogenic activity [88]. Hence, it also has been called a phytoestrogen, a mycoestrogen and a growth promotant [7]. It is produced by species of the genus *Fusarium* such as *F. graminearum*, *F. culmorum* [89]-[91], *F. equiseti* and *F. crookwellense* [7]. Zearalenone is found worldwide as a contaminant in cereals and grains, including maize [92] [93]. Despite its low acute toxicity and carcinogenicity [7], zearalenone exhibits estrogenic and anabolic properties [94]. In relation to the toxic effects in human beings, it has been claimed that premature puberty in Puerto Rico [95] and in children aged between 7 and 8 years [96] might be due to zearalenone and related compounds in the human diet. Some reports have shown the occurrence of zearalenone in food products based on maize [93]. Meucci *et al.* [97] detected the

Figure 5. The chemical structure of fumonisin B1.

Figure 6. The chemical structure of zearalenone.

zearalenone derivatives α-zearalenol and β-zearalenol in some milk samples as infant foods. In addition, Bandera *et al*. [98] detected the zearalenone in urine in 78.5% of the New Jersey girls that intake beef and popcorn. They suggested that zearalenone may exert anti-estrogenic effects similar to those reported for isoflavones. The harmful effects of zearalenone may be increased through its derivatives, α-zearalenol, β-zearalenol, α-zearalanol and β-zearalanol. Zearalenone and its derivatives have the remarkable ability to mimic estrogen, acting as an estrogen receptor agonist [99]-[101]. In addition, zearalenone has been found to suppress the activation of NFκB, the major transcription factor associated with the production of pro-inflammatory cytokines and enzymes [102].

3.6. Ergot Alkaloids

Ergot alkaloids are a complex family of indole-derived alkaloids, which are derived from the amino acid tyrptophan [103] [104]. They are produced primarily by several species of *Claviceps* (e.g. *C. purpurea*) that are plant pathogenic, and elaborate their toxins in specialized masses of fungal tissue called sclerotia [24]. These pathogenic fungi infect grain, and especially rye is very susceptible because of its open-pollinated grain [105]. In addition, there are other alkaloids-producing fungi such as *Balansia* spp. [106], *Penicillium citrinum* [107], *Neotyphodium* spp. [108] and *Aspergillus fumigatus* [104] [109]. According to their chemical similarities, ergot alkaloids can be divided into four major groups: the clavines, the lysergic acids, the lysergic acid amides and the ergopeptines [110]. All ergot alkaloids can be considered as derivatives of the tetracyclic compound 6-methylergoline [111]. Consuming grains or grain products contaminated with the sclerotia of the fungus leads to gangrenous and convulsive (neurological) forms of ergotism known as St. Anthony's fire or holy fire [7]. Ergotism is one of the oldest mycotoxicoses known, although occurrence of the disease has declined over time [24]. The gangrenous form of ergotism affects the blood supply to the extremities, while convulsive ergotism affects the central nervous system [14] [112]. Ergotamine (**Figure 7**) and its derivatives share structural similarities with the adrenergic, dopaminergic and serotonergic neurotransmitters and therefore have wide-ranging effects on the physiological processes that they mediate [113]. On the other hands, many of ergot alkaloids are pharmacologically active and are consequently used as drugs [103].

3.7. Other Mycotoxins

Fungi are potential source of several other toxic secondary metabolites such as citrinin, patulin, roquefortine C, PR toxin, cyclopiazonic acid and beauvericin. Citrinin is a yellow mycotoxin produced by several species of *Penicillium* (e.g. *P. verrucosum* and *P. camemberti*) and *Aspergillus* (e.g. *A. terreus*, *A. niveus* and *A. oryzae*) [114]. Recently, citrinin has also been isolated from industrial species used to produce red pigments *Monascus ruber*
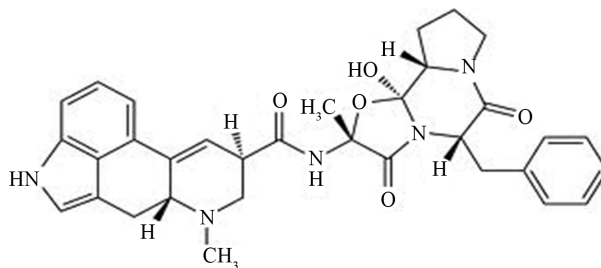
Figure 7. The chemical structure of ergotamine.

and *Monascus purpureus* [115]-[117]. Like ochratoxin A, citrinin is a nephrotoxin and can act synergistically with ochratoxin A to depress RNA synthesis in murine kidneys [118]. Chagas *et al*. [119] found that citrinin has an effect on Ca^{2+} transport in isolated kidney cortex and liver mitochondria, and baby hamster kidney cultured cells. It is significantly inhibited the activity of 2-oxoglutarate and pyruvate dehydrogenases in both kidney cortex and liver mitochondria. Patulin is a polyketide produced by several species belonging to *Penicillium*, *Aspergillus*, *Paecilomyces* and *Byssochlamys*. It is the most common mycotoxin found in apples and apple-derived products such as juice, cider, compotes and other food intended for young children [120]. It was first isolated as an antimicrobial agent during the 1940s from *Penicillium patulum* (now called *Penicillium griseofulvum*). Due to its toxicity to humans and animals, patulin was reclassified as a mycotoxin during the 1960s [7]. Exposure to patulin is associated with immunological, neurological and gastrointestinal outcomes [120]. Roquefortine C has received attention because of its neurotoxic properties [121]. It is produced by *P. roqueforti* and *P. crustosum*. PR toxin inhibits RNA and protein synthesis [122], the activities of the DNA polymerases *α*, *β* and *γ*, and mitochondrial respiration and oxidative phosphorylation in animal cells [123]. Cyclopiazonic acid is an indole tetramic acid produced by several species of *Penicillium* (e.g. *P. aurantiogriseum*) and *Aspergillus* (e.g. *A. flavus*). It is a specific inhibitor of calcium-dependent ATPase in the sarcoplasmic reticulum that results in altered cellular Ca^{2+} levels [124]. In addition to cyclopiazonic acid, *A. flavus* can produce a toxin called aflatrem contributing to the toxicity of *A. flavus*-infected crops. This toxin is a potent tremorgenic mycotoxin known to lead to neurological disorders [124]. Beauvericin is a cyclic hexadepsipeptide first studied for its insecticidal properties [125], and occurs naturally on corn and corn-based foods and feeds [126]. It is produced by some *Fusarium* species (e.g. *Fusarium proliferatum*, *F. semitectum* and *F. subglutinans*). Beauvericin is a specific cholesterol acyltransferase inhibitor [127] and is toxic to human cell lines of myeloid origin [128]. Various metabolites produced by *A. fumigatus* which may act as toxins in the host cell include fumagillin, fumigacin (helvolic acid), fumitremorgins, phthioic acid and gliotoxin. Gliotoxin in particular has been fingered as a likely virulence factor due to its cytotoxic [129], genotoxic [130] and apoptosis stimulating properties [131]. More recently, there is a novel mycotoxin named acrebol, consisting of two closely similar peptaibols, has been isolated from an indoor strain of the fungus *Acremonium exuviarum*, and it was found that inhibited complex III of the respiratory chain of the tested rat liver mitochondria [132].

4. Fungal Metabolites Involved in Mycoses

Human mycoses are caused by true fungal pathogens and opportunistic pathogens. Mycoses range from merely annoying (e.g. athlete's foot) to life-threatening (e.g., invasive aspergillosis). Pathogenicity of a fungus depends on its ability to adapt to the tissue environment and to withstand the lytic activity of the host's defenses [2] [7]. There are many metabolites produced by pathogenic fungi involving in mycoses. These metabolites are enzymes, siderophores, pigments and others.

4.1. Extracellular Enzymes

Fungi can produce and release several hydrolytic enzymes such as proteinases, lipases and phospholipases in culture media. These enzymes play a key role in fungal metabolism and may be involved in fungal pathogenesis, causing damage to the host tissues and providing nutrients in a restricted environment [133]. Production of proteinases, phospholipases and lipases by dermatophytes, *C. albicans*, *A. fumigatus* and *C. neoformans* is considered to be the fungal-associated factor that helps fungi in nutrient uptake, tissue invasion, adherence, dissemi-

nation inside the host, overcoming the host immune system and strongly contribute to fungal pathogenicity [134]. **Table 2** lists the major enzymes contributing the fungal pathogenicity. Dermatophytes produce proteinases such as keratinase and elastase playing important role in the pathogenicity of these fungi through keratin damage and elastin destruction due to secretion of two enzymes, respectively [2]. Endospores of *Coccidioides immitis* secrete proteinases with elastase and collagenase activity. These enzymes were found in culture filtrates of fungus and might play an essential role in the pathogenesis of coccidioidomycosis [135]. Proteinase-deficient strains of *Candida albicans* are non-invasive [136], and the pattern of adherence also reflects the expression of secretory proteinase [137]. Salivary proteins, including IgA, can be almost completely degraded by acidic proteinases called aspartic proteinases (Saps) of this yeast especially under low pH conditions [138]. Therefore, aspartic proteinases are of particular interest as virulence factors in the pathogenesis of *Candida* infections [139]-[141]. Hube and Naglik [142] demonstrated the production of Sap1-8 proteinases during oral and vaginal candidiasis. The results indicated that Sap1, Sap3, Sap4, Sap7 and Sap8 expression was correlated with oral disease, whereas Sap1, Sap3 and Sap6-8 expression was correlated with vaginal disease. Aspartic proteinase production is increased by *C. albicans* isolated from later stages of HIV infection and may contribute to candidosis [143]. *A. fumigatus* also secretes an aspartic proteinase (aspergillopepsin F) that can catalyze hydrolysis of the major structural proteins of basement membrane, elastin, collagen and laminin in the lung of a host [144]. By the immunogold electron microscopy, these authors showed that the aspartic proteinase was secreted by *A. fumigatus* invading neutropenic mouse lung and its secretion was directed toward the germ tubes of penetrating hyphae.

Extracellular phospholipase exhibits phospholipase B, lysophospholipase and lysophospholipase transacylase activities [145]. This enzyme can result in destabilization and destruction of the membranes and lung surfactant, cell lysis and release of lipid second messengers [146] [147]. Also, this enzyme enhances the adhesion of *C. neoformans* cells to the lung epithelium [148]. Lipase is another enzyme associated with the pathogenicity of *Malassezia furfur* that cause pityriasis versicolor. This association is showed by studies of Neves *et al*. [149] on

Table 2. Enzymes produced by some pathogenic fungi and their roles in pathogenesis.

Enzyme	Fungal pathogen	Role in pathogenesis
Elastase	Dermatophytes	Destruction of elastin in tissues
	Coccidioides immitis	Destruction of elastin in lung and blood vessels
Collagenase	*C. immitis*	Break the peptide bonds in collagen.
Elastase-alkaline serine proteinase	*Aspergillus fumigatus*	Degradation of elastin in lung tissues
Keratinase	Dermatophytes	Damage of keratin in epidermis of the skin
Aspartic proteinase	*Candida albicans C. tropicalis C. parapsilosis C. lusitaniae A. fumigatus Cryptococcus neoformans*	Destroying cell membranes and degrading host surface molecules contributing host tissue invasion and dissemination
Phospholipase	Dermatophytes *Aspergillus* spp. *C. neoformans C. albicans Trichophyton rumrum Microsporum canis Fonsecaea pedrosoi*	Cleavage of phosphodiester bond in membrane lipids for invasion
Lipase	*Malassezia furfur F. pedrosoi Phialophora verrucosa Cladosporium carrionii Cladophialophora bantiana Exophiala jeanselmei*	Degradation of lipids on the skin
Catalase	*Aspergillus* spp. *Histoplasma capsulatum C. albicans*	Protection from oxidative killing in macrophages
Superoxide dismutase	*Aspergillus* spp. *C. albicans*	Prevention from oxidative damage in macrophages
Urease	*C. neoformans, F. pedrosoi P. verrucosa, C. carrionii C. bantiana, E. jeanselmei*	Hydrolysis of urea to carbon dioxide and ammonia

fungal isolates from human healthy skin and with macules. Cryptococcal invasion of the central nervous system may be facilitated by urease production. Olszewski *et al*. [150] suggested that urease production by *C. neoformans* facilitates blood capillaries sequestration and disruption of endothelial cells and, in consequence, crossing the blood-brain barrier via a paracellular mechanism. *C. neoformans* is also able to acquire iron from its environment during host infection via enzymatic system. The production of urease also shows a positive correlation with the pathogenicity of other fungal agents causing diseases in humans, such as *C. immitis* [151] and *P. brasiliensis* [152].

A recent study demonstrated that *C. neoformans* was able to secrete vesicles containing many of enzymes, including laccase, urease and phospholipase B [153]. During disseminated cryptococcosis, measurable levels of cryptococcal products are detected in the body fluid of patients [154], suggesting that these vesicles may represent an efficient and general way of delivering pathogenesis-related metabolites to the extracellular environment by *C. neoformans* [153]. Dimorphism is a fungal characteristic which depends on alteration of body temperature, osmotic stress, oxidative stress and certain human hormones and helping the fungus to withstand the aggression by the host. Dimorphism-regulating histidine kinase enzyme in dimorphic molds such as *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *C. immitis* can cause them to switch from their non-virulent mold forms to their virulent yeast forms. It also triggers the yeast *C. albicans* to switch from its yeast form to its more virulent hyphal form [2]. In iron gathering, *C. neoformans* and *H. capsulatum* reduce ferric to ferrous with a ferric reductase present at the fungal cell surface. This process is followed by transport of the ferrous ions into the cell by a permease and ferroxidase complex connected with the plasma membrane and ultimately enhancing fungal growth [155] [156]. To overcome the host defense mechanism, superoxide dismutase and catalase are produced by *C. albicans* [157] and *A. fumigatus* [158] when exposed to reactive oxygen species produced by phagocytic cells.

4.2. Siderophores (Iron Chelators)

Iron element is required for growth of the vast majority of microorganisms, because it serves as a catalytic cofactor in oxidation-reduction reactions [159] [160]. In the aerobic environments, iron exists mainly as Fe (III) and tends to form insoluble hydroxides and oxyhydroxides [160] [161], making it largely unavailable to fungi. In the human body, the majority of iron is bound up in hemoglobin, though other proteins bind iron directly, including transferrin, lactoferrin and ferritin, so the free iron concentration is extremely low insufficient for fungal growth [160]. Therefore, fungi need mechanisms to solubilize Fe(III) to make it available for uptake. These mechanisms usually involve the production of siderophores. Siderophores are low molecular weight (500 - 1000 Da), high affinity ferric iron-chelating compounds produced by all microorganisms including fungi, with the exception of *Saccharomyces* spp. and obligate anaerobic bacteria which do not produce them [8] [162], although *Saccharomyces cerevisiae* and some pathogenic yeasts (e.g. *Cryptococcus neoformans* and *C. albicans*) can use exogenous siderophores [163]. Siderophores are very important to solubilize and transport inorganic iron [164]. In comparison with bacterial siderophores containing a variety of functional groups [165, most fungi produce hydroxamate-type siderophores [8] [166]. However, the zygomycetes form iron-regulated polycarboxylates [167], and there are well-documented reports of phenolate-catecholates in species of the wood-rotting fungi [168]. The mechanisms of fungal pathogenesis are much less-well understood than are those of bacterial pathogens [169]. Recent reports show that iron plays an important role in the virulence of pathogenic fungi [170] [171]. Because fungal iron supply systems are crucial in overcoming the iron shortage imposed by the host, most fungi express specific mechanisms for the acquisition of iron from the hosts they infect for their own survival [172]. Recently, siderophore biosynthesis has been found to be crucial for fungal pathogenicity [173]. Siderophores secreted by pathogenic fungi are critical for their survival in mammalian hosts whose iron homeostasis is strictly regulated [174]. They have biosynthesized by many human pathogens such as *Cryptococcus neoformans* [155], *H. capsulatum* [166] [175], *Aspergillus fumigatus* [176] [177], *B. dermatitidis*, *Sporothrix schenickii*, *C. albicans* and *Trichophyton mentagrophytes* [166], and are essential for virulence in host-fungus interactions. In addition to transporting iron and pathogenicity, siderophores have other functions and effects, including, acting as intracellular iron storage compounds, thereby preventing the formation of free radicals which are formed by unbound iron [8] [178] and suppressing growth of other microorganisms [8]. Fungal-siderophores structures, their functions and applications are well reviewed by Renshaw *et al*. [8].

4.2.1. Hydroxamates

Other than zygomycetes, most ascomycetous and basidomycetous fungi can synthesize hydroxamate-type siderophores containing N^5-hydroxy-N^5-acyl-L-ornithine residues as a basic structural units which constitute the iron binding ligands [179]. Virtually all of the fungal hydroxamate siderophores characterized so far are derived from L-ornithine and biosynthesis of siderophores is regulated by an internal iron-sensing mechanism [8]. Fungal hydroxamates can be divided into three structural categories: fusarinines, coprogens and ferrichromes. Each hydroxamate groups provides two oxygen molecules, which form a bidentate ligand with iron.

 1) Fusarinines

 Fusarinines are either linear (dimers or trimmers) or cyclic trimers hydroxamates in which *N*-hydroxyornithine is *N* acylated by anhydromevalonic acid [180] [181]. Except neurosporin, fusarinines are made of *cis*-fusarinine units [182]. The monomers *cis*- and *trans*-fusarinine are the structural units of a large number of fungal siderophores [182]. There are three types of fusarinines, fusarinine A (linear dimers), fusarinine B (linear trimers) and fusarinine C (cyclic trimmers, also called fusigen) [8]. Among zoopathogenic fungi, various fusarinines are found in *H. capsulatum* [183], *Paecilomyces* spp., *Aspergillus* spp., *Fusarium* spp. [180] and *Epicoccum purpurescens* [184].

 2) Coprogens

 Coprogens are linear dihydroxamate and trihydroxamate ligands composed of *trans*-fusarinine units [185]. They are produced by *H. capsulatum* [183], *B. dermatitidis* [186], *Fusarium dimerum* and *Curvularia lunata* [180].

 3) Ferrichromes

 Ferrichromes are cyclic peptides containing N-δ-acyl-N-δ-hydroxyornithine and combinations of glycine, serine or alanine. They are the most common fungal siderophores [187], and produced by *Trichophyton* spp. [188], *Microsporum* spp. [188] [189] and *Aspergillus* spp. [180] [185]. In addition to their roles in iron solubilization and transporting, ferrichromes are intracellular iron storage molecules.

4.2.2. Carboxylates

Although most of the fungal siderophores are hydroxamates, a new carboxylate siderophore, rhizoferrin, has been detected [190]. Rhizoferrin functions as the main siderophore of the Zygomycetes. Its production, isolation and structure have described by Drechsel *et al*. [191]. Zygomycosis (also called mucormycosis) is a fungal infection caused by fungi belonging to Zygomycetes. In this context, zygomycosis may be associated with rhizoferrin production. Therefore and to show this association, further studies are required.

5. Pigments

5.1. Melanins

Melanins (**Figure 8**) are negatively charged, hydrophobic darkly pigmented polymers (brown or black in color) formed by oxidative polymerization of phenolic or indolic compounds [192]-[194]. The phenolic compounds from which the fungal melanins are derived include tyrosine via 3, 4-dihydroxyphenylalanine (DOPA) in various fungi and other microorganisms, γ-glutaminyl-3,4-dihydroxybenzene or catechol in basidiomycetes and 1,8-dihydroxynaphthalene (DHN) in ascomycetes and related deuteromycetes [195]. Melanins are made by several pathogenic fungi with several different types, but the two most important types are DHN (1,8-dihydroxynaphthalene) and DOPA (3,4-dihydroxyphenylalanine) melanins, which have been implicated in pathogenesis [194] [196] [197]. Fungal melanins are usually found in the cell walls of spores, sclerotia, mycelia or fruiting bodies [198]. Even when not directly involved in pathogenesis, melanins provide structural strength [199] and protect fungi against environmental stresses such as oxygen free radicals [200], UV radiation [201]-[204], wall-degrading enzymes produced by antagonist microbes [205] [206], high salinity [207] and heavy metals toxicity [208]. It has been suggested that due to antioxidant property of melanins they can neutralize oxidants produced by immune effector cells. Phagocytic leukocytes kill pathogenic microorganisms with a flux of secreted strong oxidants [209]. Thus, any microbial product which neutralizes oxidants is likely to protect the pathogen and promote invasion. Within the human body, fungal melanins can neutralize antimicrobial oxidants generated by immune effector cells [210]. The pathogenic yeast *Cryptococcus neoformans* serves as an example of how melanin production increases virulence. Several types of evidence support the antioxidant role of melanin in this yeast [211]-[214], *i.e.* the interference of melanins with oxidative metabolism of phagocytosis making
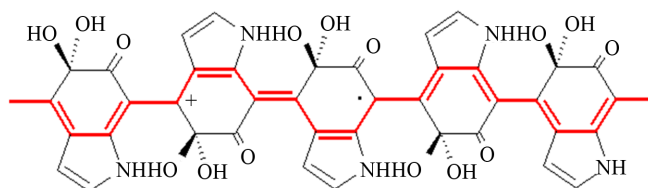
Figure 8. The chemical structure of melanin.

the fungus relatively resistant to leukocyte attack. The pathogenic roles for fungal melanins have been reviewed by Jacobson [194]. In addition to synthesis of melanin *in vitro*, some pathogenic fungi such as *C. neoformans* [215], *Paracoccidioides brasiliensis* [216] and *C. albicans* [217] can synthesize melanin during infection (*in vivo*), which has important implications for pathogenesis and antifungal drug development. Although much attention has been focused on the role of melanin in *C. neoformans*, this substance is constitutively produced in other pathogenic fungi in a group called dematiaceous fungi causing invasive disease called phaeohyphomycosis [218]. Dematiaceous fungi are a heterogeneous group of organisms unified by their production of melanin pigments [219]. The diseases caused by dematiaceous fungi have been reviewed by McGinnis *et al*. [220], Revankar [221] and Revankar *et al*. [222]. Due to protective role of fungal melanin, dematiceous fungi are extremely difficult to treat with antifungal drugs [223]. **Table 3** lists the melanin-producing fungi which consist of both opportunistic and true pathogenic strains. As demonstrated by Cutler and Swatek [224], da Silva *et al*. [225], Dixon *et al*. [226], Jahn *et al*. [227] and Romero-Martinez *et al*. [200], melanins seem to be important in initiating an infection, because melanin-deficient (albino) fungi are much less infective.

5.2. Carotenoids

Carotenoids are a family of yellow to orange-red tetraterpenoid pigments synthesized by photosynthetic organisms, as well as many bacteria and fungi. They protect these organisms against photooxidation. They effectively quench singlet oxygen, *i.e.*, they absorb energy from singlet oxygen ($^1O_2$) and convert it back into the unexcited ground state [228]. Carotenoids are produced by some pathogenic fungi such as the yeast *Wangiella* (*Exophiala*) *dermatitidis* that synthesizes, besides melanin, the carotenoids torulene (3,4-didehydro-g-carotene) and torularhodin (3,4-didehydro-β,γ-caroten-16-oic acid) [229]. As demonstrated by Geis and Szaniszlo [229], these carotenoids significantly increase post-UV irradiation survival rates of the melanin-deficient *W. dermatitidis* strain Mel⁻4. They suggested that the mechanism of carotenoid action is more likely to consist in shielding sensitive molecules or organelles rather than in neutralization of harmful oxidants. The influence of these carotenoids on the virulence of this yeast has also been studied by Schnitzler *et al*. [230]. They found that torulene and torularhodine were not contributed to the prevention of killing by neutrophils. Dixon *et al*. [226] [231] [232] observed a reduced virulence in mice when melanin- and carotenoids-deficient *W. dermatitidis* 8656 (Mel⁻3) strain was used, suggesting that the reduced virulence of this mutant is due to a lack of melanin and/or the carotenoids. *Rhodotorula* is a basidiomycetous yeast that produces mucoid colonies with a characteristic carotenoid pigment and is widely distributed in the environment. Although regarded as non-pathogenic, *Rhodotorula* species have emerged as opportunistic pathogens with the ability to colonize and infect susceptible patients. Most cases of *Rhodotorula* infection are fungemia associated with catheters, endocarditis and meningitis. *Rhodotorula rubra* is the most common cause of *Rhodotorula* species fungemia, followed by *R. glutinis* and *R. minuta* [233]. In general, there are very little information available concerning the involvement of carotenoids in fungal pathogenesis and further studies are required.

6. Other Metabolites

A number of other metabolites such as pullulan, mannitol, β-(1,3)-glucan, hem-binding proteins, estrogen-binding proteins and others could be a part of virulence factors contributing in fungal pathogenesis. These metabolites were listed in **Table 4**. *Aureobasidium pullulans* is potentially pathogenic yeast especially in immunocompromised patients [234]. Infections can range from subcutaneous to deep tissue. Severe infections have been noted such as in the serous membrane of the abdominal cavity [235] and in the spleen [236]. Niedoszytko *et al*. [237] concluded that sensitization to *A pullulans* is a risk factor for severe asthma. *A. pullulans* produces and se-

Table 3. Melanin-producing fungi and related diseases.

Fungus	Disease
Aspergillus fumigatus[a]	Invasive aspergillosis
A. nidulans[a]	Invasive aspergillosis
A. niger[a]	Invasive aspergillosis
Alternaria alternate[a]	Allergic reactions
Alternaria tenuissima[a]	Cutaneous infection
Aureobasidium pullulans[a]	Nosocomial infection asthma, peritonitis
Bipolaris spicifera[a]	Phaeohyphomycosis
Blastomyces dermatitidis[b]	Blastomycosis
Cladosporium carionii[b]	Chromoblastomycosis
Cryptococcus albidus[a]	Cutaneous cryptococcosis
C. laurentii[a]	Cutaneous cryptococcosis
C. curvatus[a]	Cryptococcosis
C. neoformans[a]	Pulmonary cryptococcosis
C. gattii[a]	Cryptococcosis
Dactylaria gallopava[a]	Cerebral phaeohyphomycosis
Exophiala jeanselmei[a]	Subcutaneous phaeohyphomycosis
Fonsecaea compacta[a]	Chromoblastomycosis
Fonsecaea pedrosoi[a]	Chromoblastomycosis
Histoplasma capsulatum[b]	Histoplasmosis
Paracoccidioides brasiliensis[b]	Paracoccidioidomycosis
Penicillium marneffei[a]	Penicilliosis
Hortaea werneckii[b]	Tinea nigra
Phialophora richardsiae[a]	Subcutaneous infections
Scytalidium dimidiatum[a]	Skin and nail infections
Sporothrix schenckii[b]	Sporotrichosis
Wangiella (Exophiala) dermatitidis[a]	Phaeohyphomycosis
Xylohypha bantiana[a]	Cerebral phaeohyphomycosis
Scedosporium prolificans[a]	Invasive and disseminated infections
Lacazia loboi[b]	Lobomycosis
Pneumocystis carinii[a]	Pneumonia

[a]Means opportunistic pathogen; [b]Means true pathogens.

cretes the polysaccharide pullulan and other biomacromolecules [238]. These molecules may play important roles in mediating adhesion and attachment on host cells playing a critical role in infection. The dimorphism of some pathogenic fungi is related to the cell wall components.

In the mycelial form, there is a predominance of β-(1,3)-glucan, whereas in the yeast form the main polysaccharide is α-(1,3)-glucan [13]. Studies carried out on *P. brasiliensis* isolates have suggested that α-(1,3)-glucan protects the fungus against digestive enzymes of the host phagocytes [239]. α-(1,3)-glucan is also found in other

Table 4. Some fungal metabolites, their source and their roles in pathogenesis.

Metabolite	Fungus	Role in pathogenesis
β-(1,3)-glucan	*Paracoccidioides brasiliensis* *Blastomyces dermatitidis* *Histoplasma capsulatum*	Protection the fungi against digestive enzymes of the host phagocytes
Mannitol	*Cryptococcus neoformans*	Protection the fungi against oxidative killing by host phagocytes
Pullulan	*Aureobasidium pullulans*	Mediating adhesion and attachment on host cells
Estrogen-binding proteins	*Coccidioides immitis*	Accelerate spherule maturation and endospore release
Hem-binding proteins	*Candida albicans*	Enabling the fungus to utilize hemin and hemoglobin as iron sources.
Agglutinin-like sequence (Als) proteins	*C. albicans*	Mediating adhesion on host cells
Farnesol	*C. albicans*	Affect host immunity
WI-1 protein	*Blastomyces dermatitidis*	Mediating adhesion on macrophages
Glycoprotein (gp4)	*P. brasiliensis*	Mediating attachment on macrophages
Glucuronoxylomannan (GXM)	*C. neoformans* *Trichosporon beigelii*	Immunosuppressive agent

pathogenic fungi such as *B. dermatitidis* and *H. capsulatum*, conferring higher rigidity to the cell wall and resistance to the attack of phagocytes [240] [241].

Mannitol is another metabolite which may be considered as virulence factor involved in fungal pathogenicity. Infection of the central nervous system caused by *C. neoformans* is often associated with production of a large amount of mannitol by this fungus [242]. This process may facilitate the development of meningoencephalitis, because mannitol increases the osmolality of the surrounding fluid, thus it may contribute to brain edema, and also prevents oxidative damage to the fungus [243]. Mannitol can protect the fungi from oxidative killing by neutrophils or by cell-free oxidants [244]. Mannitol production is also thought to be helpful for *C. neoformans* to resist other environmental stresses such as heat and osmotic stresses [245]. They showed that a *C. neoformans* mutant producing low levels of mannitol was more susceptible to heat and osmotic stresses.

C. albicans has plasma membrane-anchored proteins called hem-binding proteins enabling this fungus to utilize hemin and hemoglobin as iron sources. If these proteins are absent, iron metabolism in this fungus is severely affected [246]. In addition, the cell wall of this fungus has agglutinin-like sequence proteins (Als proteins) as adhesion molecules. By these proteins *C. albicans* has flexibility and adaptability and can invade different environments in the host [247]. A protein called WI-1 present on the surface of *B. dermatitidis* plays the role of an adhesin and is believed to favor adherence of the fungus to macrophages [248]. The surface glycoprotein (gp43) of *P. brasiliensis* seems to be related to the fungal pathogenesis. It is the major laminin-binding protein helping the yeast form of this fungus in attachment to macrophages [249]. Other adhesion molecules were reviewed by [134].

In iron limitation, *C. neoformans*, beside to ferric reductase, also secretes 3-hydroxyanthranilic acid which reduces ferric to ferrous for transport by a copper oxidase permease system [250]. Therefore, these metabolites play important roles in pathogenicity of this yeast.

Estrogen-binding proteins in the cytosol of *C. immitis* may represent virulence factors for this fungus. In this fungus these proteins accelerate spherule maturation and endospore release [2].

Farnesol is the first identified fungal and eukaryotic quorum sensing molecule. It is responsible for the regulation of yeast to mycelium conversion in *C. albicans*. Navarathna *et al.* [251] found that the cells programmed to secrete more farnesol were significantly more virulent than untreated *C. albicans*. With these findings, they concluded that the fungal quorum sensing molecule farnesol is a virulence attribute in candidiasis. They observed that farnesol altered the normal cytokine expression pattern in mice in a fashion favoring disease progression.

Navarathna *et al.* [252] concluded that farnesol inhibits the production of IL-12 p40 and p70 from IFN-gamma/LPS-stimulated macrophages. Therefore, the role of farnesol in systemic candidiasis is likely due to its ability to inhibit the critical Th1 cytokines IFN-gamma and IL-12 and perhaps to enhance a Th2 cytokine, IL-5.

Glucuronoxylomannan (GXM) is the major component of *Cryptococcus* capsular polysaccharide (about 90% - 95% of capsule), which represents an essential virulence factor that has multiple effects on host immunity [253]. In macrophages, *C. neoformans* releases GXM from its capsule during its replication and into vesicles around the phagosome of the host cell resulting in macrophage dysfunction and lysis [254]. Several publications have demonstrated that GXM has multiple effects. It shows potent immunosuppressive properties such as interference with neutrophil migration [255], interference with cytokine secretion [256], inhibition of T-cell proliferation [257], induction of macrophage apoptosis mediated by either Fas ligand [256] or by nitric oxide (NO) generation [253], induction of apoptosis in T cells [258] and delay maturation and activation of human dendritic cells [259]. In addition, high levels of GXM in the cerebrospinal fluid (CSF) can change the osmolarity of this fluid, thereby affecting its outflow and leading to increased intracranial pressure, headaches and visual disturbance [260].

A glucuronoxylomannan-like polysaccharide was detected in sera of patients with systemic infections caused by the opportunistic fungus *Trichosporon beigelii* through cross-reaction with anticryptococcal antibodies [261]. They found that pathogenic isolates from deep infections produced significantly more antigen than superficial or environmental isolates supporting the idea that this antigenic polysaccharide may be a virulence factor for this fungus.

The failure of phagocytes to interact with *T. beigelii* may be related to a surface component or components which restrict phagocyte-*T. beigelii* interaction [261].

7. Conclusion

According to the review of the literature on fungal mycopathy, it is clear that there are many metabolites with different roles in mycoses. All these metabolites make this eukaryotic group successful for the survival in a host thereby interacting and overcoming the host immune system. Some metabolites such as mycotoxins are reported widely and are of general concern, because they can cause mycotoxicoses in humans and animals. The sources and properties of these compounds have been highlighted in this review. Several extracellular enzymes such as proteases, lipases and phospholipases are very important virulence factors. These enzymes play a role in nutrition, tissue damage, dissemination within the human body, iron acquisition, overcoming the host defenses and strongly contribute to fungal pathogenicity. Iron chelating compounds (siderophores) are produced by many fungal pathogens to support their survival in mammalian hosts whose iron homeostasis is strictly regulated. Melanins are made by several pathogenic fungi with several different types and have been implicated in pathogenesis. They can neutralize oxidants produced by immune effector cells. Other fungal metabolites such as melanins, carotenoids and others as reviewed above were recorded to be virulence factors involved in fungal pathogenicity. We can conclude that the knowledge of the fungal pathogenicity and molecular basis of their virulence contributes in developing new strategies for treatment and new effective antifungal agents. Finally, the many properties of metabolites support a wide variety of functional models, and new and imaginative pathogenic hypotheses are needed.

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